EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF QUIZALOFOP-ETHYL

REPRODUCTIVE AND CANCER HAZARD ASSESSMENT SECTION

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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Basis for Consideration of Quizalofop ethyl

- Formal identification by the U.S. Environmental Protection Agency as causing (male) reproductive toxicity

- After publication of a Notice of Intent to List, referred to the DART Committee because the data used by the authoritative body did not meet the criteria specified in regulations

Quizalofop-ethyl

- Phenoxypropionic acid ester
- [(2-(4-((6-chloro-2-quinoxalinyl)oxy)phenoxy)-ethyl ester]
- $C_{19}H_{17}ClN_2O_4$ (Molecular weight 372.81)

Uses

- Formerly used as a herbicide on broadleaf crops
- Not registered for use in California since 1993

Developmental effects

- Human data: none identified
- Animal data: 3 studies

- *Rabbits: 1 study*
  * orally exposed on days 6-18 of gestation, no adverse developmental effects (high dose mildly toxic to the dams)

Developmental effects (cont.)

- *Rats: 2 studies*
- Developmental toxicity study
  * orally exposed on days 6-15 of gestation
  * lower fetal survival at day 21 at the highest dose tested ($p<0.05$)
  * higher incidence of skeletal variations at the high ($p<0.001$) and mid ($p<0.05$) doses

Developmental effects (cont.)

- Developmental toxicity study (continued)
  * lower postnatal bodyweight and food intake in high dose offspring
  * lower absolute ($p<0.01$) and relative ($p<0.05$) uterine weights in high dose female offspring at age 8 weeks
  * No effects on reproductive function at age 10 weeks in animals treated *in utero*

Developmental effects (cont.)

- 2-generation reproductive toxicity study
  * decreased percentage or number of pups born alive in the F_{1A} and F_{2A} high-dose litters
  * decrease birthweights in the high-dose litters in the F_{1A} and F_{1B} groups
  * decrease early postnatal weights in the high-dose litters in the $F_{1A,}F_{1B}$ and F_{2B} groups

Developmental effects (cont.)

- 2-generation reproductive toxicity study (continued)
  * increased incidence of hemangioma in all treatment groups (F_{1B} generation) and the mid- and high-dose groups (F_{2A} generation)

Female reproductive effects

- Human data: none identified
- Animal data:
- One 2-generation reproductive toxicity study in rats, one study in rats of effects of *in utero* exposure on reproductive function
- Five studies of potential reproductive organ effects

Female reproductive effects (cont.)

- *Rats: 2-generation reproduction study*
  * Significant decrease in fertility index in low-dose dams of the F_{1A} generation (no effect on mid- and high-dose dams in this generation, no effect on any dose groups in other generations)

Female reproductive effects (cont.)

- *Dogs: 2 subchronic studies*
  * uterine and ovarian weights varied from control values, no apparent dose-response relationship

- *Rats: 2 subchronic/chronic studies*
  * no evidence of effects on female reproductive organs

Female reproductive effects (cont.)

- *Mice: 1 chronic study*
  * uterine and ovarian weights increased at all doses tested
  * increased incidence of ovarian hemorrhage at the high dose tested

Male reproductive effects

- Human data: none identified
- Animal data:
- One 2-generation reproductive toxicity study in rats, one study in rats of effects of *in utero* exposure on reproductive function
- 5 studies of potential reproductive organ effects

Male reproductive effects (cont.)

- *Rats: 2-generation reproduction study*
  * Significant decrease in fertility index in low-dose males of the F_0 generation (no effect on mid- and high-dose males in this generation or the F_{1A} generation
  * Single incidence of focal hyperplasia of the testis in a high-dose male in the F_{1A} group

Male reproductive effects (cont.)

- *Dogs: 2 subchronic studies*
  * 6 month study; testicular atrophy reported at high dose tested (basis for authoritative body identification of reproductive toxicity)
  * 12 month study; same design as above, more comprehensive assessment of testes did not identify any testicular atrophy

Male reproductive effects (cont.)

- *Rats: 2 studies*
  * 13 week study; high incidence of testicular atrophy at end of treatment and also after a 6 week recovery period
  * 104 week study; no testicular atrophy after exposure to approximately one third the effective dose in the earlier study

Male reproductive effects (cont.)

- *Mice: 1 chronic study*
  * 78 week study; increased incidence of testicular atrophy.
  * Bilateral atrophy increased in dose-related manner at two highest doses.
  * Combined unilateral and bilateral atrophy increased at all doses

Summary

- **Evidence for developmental toxicity of quizalofop-ethyl**

- *Developmental toxicity study (rats exposed on days 6-15 of gestation):*
  - lower fetal survival
  - higher incidence of skeletal variations

Summary (cont.)

- *Developmental toxicity study (rats exposed on days 6-15 of gestation) (continued):*
  - lower postnatal bodyweight and food intake
  - lower absolute and relative uterine weights at 8 weeks of age

Summary (cont.)

- *2-generation reproductive toxicity study (rats):*
  - decreased live births, birthweights and early postnatal weights
  - increased incidence of hemangioma in pups

Summary (cont.)

- **Evidence for female reproductive toxicity of quizalofop-ethyl:**
  - increased ovarian weights and increased incidence of ovarian hemorrhage after 78 weeks exposure in mice

Summary (cont.)

- **Evidence for male reproductive toxicity of quizalofop-ethyl:**
  - testicular atrophy in dogs exposed to quizalofop-ethyl for 6 months (but not in dogs exposed for 12 months)
  - increased incidence of testicular atrophy in rats exposed for 13 weeks

Summary (cont.)

- increased incidence of testicular atrophy in mice exposed for 78 weeks
- isolated decrease in fertility index in low-dose males of the F_0 generation only in a 2-generation reproduction study
- single incidence of focal hyperplasia of the testis in an F_1 rat from a 2-generation reproduction study